Interview Summary

Application No.	Applicant(s)	
07/967,267	Cook et al.	
Examiner	Group Art Unit	
Gary L. Kunz	1211	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Gary L. Kunz* (3) *Herb Boswell*

(2) *Joseph Lucci* (4) _____

Date of Interview *Feb 26, 1997*

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

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Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: *9 -10 and 15 - 27*

Identification of prior art discussed:
Teoule et al.; Kikuchi et al.; Buhr et al.; Sproatt et al.; Inoue et al.

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Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
The teachings of Teoule et al. regarding 2'-O-modified nucleosides was reviewed. It was pointed out that the modifications of Teoule et al. (page 4, lines 16 - 26) probably refers to an internal substitution of a carbon atom by one of the heteroatoms rather that a true substituent attached to the carbon chain itself. However, the examiner also pointed out that the sulfone and sulfoxide groups in the definition of R2 in claim 9 must represent carbon substitutions rather than a true substituent. Applicant's representatives objected to the 103 rejections on the grounds that the prior art (Sproat and Inoue) teaches that the synthesis of 2'-O-modified guanosine (other that methyl and ethyl) is problematic.

This means that the inventions were not actually in the possession of the public. The examiner agreed to fully consider a subsequent amentment to the claims.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

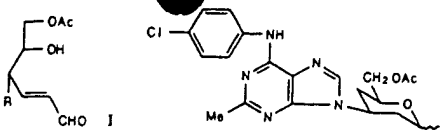
1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Gary L. Kunz

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action



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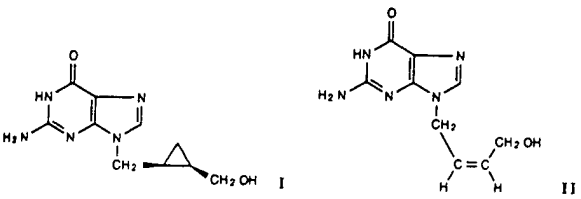
= H, OAc) underwent a Michael reaction with 6-(4-chlorophenyl)-amino)-2-methylpurine and theophylline to give isonucleosides, e.g., II.

110: 24223r **Conformational analysis of 8-substituted isopropylidene derivatives of adenosine-5'-carboxylic acid.** Timoshchuk, V. A.; Ermolenko, T. M.; Akhrem, A. A. (Beloruss. Inst. Epidemiol. Mikrobiol., Minsk, USSR). *Zh. Org. Khim.* 1988, 24(6), 1214-20 (Russ). NMR data confirms that for 2',3'-*O*-isopropylidene derivs. of adenosine 5'-carboxylic acid the most probable conformation is C4'-endo, O4'-exo, and C1'-endo. Compds. of this series are characterized principally by a syn-conformation of the heterocycle around the *N*-glycosidic bond relative to the ribose fragment of the mols. CD data confirmed that conformations are stabilized by a spatial convergence of the N3 heterocyclic atom and the carboxyl group.

110: 24224s **Synthesis and antiherpetic activity of (±)-9-[[(=Z)-2-(hydroxymethyl)cyclopropyl]methyl]guanine and related compounds.** Ashton, Wallace T.; Meurer, Laura Canning; Cantone, Christine L.; Field, A. Kirk; Hannah, John; Karkas, John D.; Liou, Richard; Patel, Gool F.; Perry, Helen C.; et al. (Merck Sharp and Dohme Res. Lab., Rahway, NJ 07065 USA). *J. Med. Chem.* 1988, 31(12), 2304-15 (Eng). A series of analogs of acyclovir and



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ganciclovir were prepd. in which conformational constraints were imposed by incorporation of a cyclopropane ring or unsatn. into the side chain. In addn., several related base-modified compds. were synthesized. These acyclonucleosides were evaluated for enzymic phosphorylation and DNA polymerase inhibition in a staggered assay and for inhibitory activity against herpes simplex virus types 1 and 2 in vitro. Certain of the guanine or 8-azaguanine derivs. were good substrates for the viral thymidine kinase and were further converted to triphosphate, but none was a potent inhibitor of the viral DNA polymerase. Nevertheless, one member of this group, (±)-9-[[(*Z*)-=8-(hydroxymethyl)cyclopropyl]methyl]guanine (I), displayed significant antiherpetic activity in vitro, superior to that of the corresponding cis olefin II. Another group, typified by (±)-9-[[(*E*)-2-(hydroxymethy=l)cyclopropyl]methyl]adenine, possessed modest antiviral activity despite an apparent inability to be enzymically phosphorylated. The relationship of side-chain conformation and flexibility to biol. activity in this series is discussed.

110: 24225t **Palladium-catalyzed cross-coupling of halogeno=nucleosides with organoaluminums.** Hirota, Kosaku; Kanbe, Yoshitake; Kitade, Yukio; Maki, Yoshifumi (Gifu Pharm. Univ., Gifu, Japan 502). *Nucleic Acids Symp. Ser.* 1988, 20, 31-2 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. Cross-coupling of 8-bromoadenosine derivs. with trialkylaluminums in the presence of palladium catalyst leads to the formation of the corresponding 8-alkyladenosines. Thymidine and ribosylthymine are also prepd. by analogous reaction of 5-bromouridines with Me_3Al.

110: 24226u **Convenient synthesis of diribonucleotides.** Shimidzu, Takeo; Ozaki, Hiroaki; Yamoto, Shuhei; Honda, Kenichi (Grad. Sch. Eng., Kyoto Univ., Kyoto, Japan 606). *Nucleic Acids Symp. Ser.* 1988, 20, 83-4 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. Various kinds of sequence-defined diribonucleotides having 2'-5' or 3'-5' linkage have been synthesized.

110: 24227v **Synthesis of cyclic oligonucleotides by a modified phosphotriester approach.** De Vroom, E.; Broxterman, H. J. G.; Bliedregt, L. A. J. M.; Van der Marel, G. A.; Van Boom, J. H. (Gorlaeus Lab., 2300 RA Leiden, Neth.). *Nucleic Acids Res.* 1988, 16(10), 4607-20 (Eng). The viability of the allyl group as protection for the 3'-terminal phosphodiester function is demonstrated by its use in the synthesis of cyclic tetraribonucleotides [r(AAAA) and r(UA$_{Me2}$UA$_{Me2}$)], cyclic hexadeoxyribonucleotides [d(CGCGCG) and d(TAAAAA)] and the cyclic octadeoxyribonucleotide [d(CGTGCGTG)] by the phosphotriester method.

110: 24228w **Evaluation of the 2 NH$_2$A-T pair in hybridization. Synthesis of the DNA/RNA hybrid oligomers containing 2-aminoadenosines.** Kikuchi, Kaeko; Taniyama, Yoshio; Marumoto, Ryuji (Cent. Res. Div., Takeda Chem. Ind. Ltd., Osaka, Japan 532). *Z. Naturforsch., B: Chem. Sci.* 1988, 43(5), 623-30 (Eng). DNA decamers CGTrA'GCATGC and CGTrA'GCrA'TGC (rA' = 2-aminoadenylic acid) were synthesized. Oligonucleotide duplexes including the 2 NH$_2$A-T (2 NH$_2$A = 2-aminoadenosine) base pairs were prepd. and their melting temp. profile examd. Contrary to expectation, elevation of the melting temp. value by the 2 NH$_2$ group is very small in DNA/RNA duplexes. It appears from the CD spectra that the distortion of the B-DNA structure caused by scattered DNA/RNA base pairing diminishes the efficiency of H bonding and base stacking of the duplexes. DNA duplexes contg. 2-aminoadenosine hybrids are fairly resistant to RNase T2 or nuclease P1 digestion.

110: 24229x **A new approach to the synthesis of a protected 2-aminopurine derivative and its incorporation into oligodeox=ynucleotides containing the Eco RI and Bam HI recognition sites.** McLaughlin, Larry W.; Leong, Terence; Benseler, Fritz; Piel, Norbert (Dep. Chem., Boston Coll., Chestnut Hill, MA 02167 USA). *Nucleic Acids Res.* 1988, 16(12), 5631-44 (Eng). A protected 2-aminopurine nucleoside suitable for incorporation into oligodeoxynucleotides using phosphite triester chem. synthesis procedures was prepd. via oxidn. of a purine hydrazino deriv. with Ag_2O. Five oligodeoxynucleotides contg. Eco RI and Bam HI recognition sites were prepd. such that, in the double stranded form, the 2-aminopurine base had either a complementary thymine or cytosine nucleobase. The helix character and thermodn. parameters for helix formation were examd.

110: 24230r **Synthetic study toward oligonucleotides involving instant removal of an anilidate group from 5'-O-DMTr-2'-=deoxyribonucleoside phosphoroanilidates through nitrites-acetic anhydride.** Nishino, Shigeyoshi; Nagato, Yasuhiro; Hasegawa, Yoshihiro; Kamaike, Kazuo; Ishido, Yoshiharu (Fac. Sci., Tokyo Inst. Technol., Tokyo, Japan 152). *Nucleic Acids Symp. Ser.* 1988, 20, 73-4 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. Treatment of 5'-*O*-dimethoxytrityl-2'-deoxy=ribonucleotide phosphoroanilidate deriv. with tetrabutylammonium nitrite (3 mol. equiv.) - acetic anhydride (4 mol. equiv.) in pyridine at room temp. removed the anilidate protecting group, and is practically useful in oligonucleotide synthesis so far as a succinyl protecting group is used for the amino group on the nucleic acid base moieties.

110: 24231s **Allylic protecting groups in solid-phase DNA synthesis.** Hayakawa, Yoshihiro; Wakabayashi, Shigeharu; Noyori, Ryoji (Chem. Instrum. Cent., Nagoya Univ., Nagoya, Japan 464-01). *Nucleic Acids Symp. Ser.* 1988, 20, 75-6 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. The efficiency of allyl and allyloxycarbonyl protecting groups for internucleotide linkages and nucleoside bases, resp., in solid-phase synthesis of DNA oligomers is demonstrated.

110: 24232t **Solid-phase synthesis of polyribonucleotides using a new acetal group for the protection of 2'-hydroxyl function.** Sakatsume, Osamu; Ohtsuki, Michiya; Takaku, Hiroshi; Reese, Colin B. (Dep. Ind. Chem., Chiba Inst. Technol., Chiba, Japan 275). *Nucleic Acids Symp. Ser.* 1988, 20, 77-8 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. The solid phase synthesis of oligoribonucleotides using H-phosphonate approach and the 1-(2-chloro-4-methylphenyl)-4-methoxypiperidin-4-yl (Ctmp) and DMTr groups, resp., for the protection of the 2'- and 5'-hydroxyl functions is described. The convenient prepn. of nucleoside H-phosphonate units is also discussed in detail.

110: 24233u **Synthesis and properties of ribooligonucleotides which form a G:U base pair in a duplex.** Tanaka, Toshiki; Orita, Masaya; Sakata, Takeshi; Uesugi, Seiichi; Ikehara, Morio (Fac. Pharm. Sci., Osaka Univ., Osaka, Japan 565). *Nucleic Acids Symp. Ser.* 1988, 20, 79-80 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. The oligoribonucleotides with chain length of 6-9 were synthesized on a polymer support in order to investigate the three dimensional structure of RNA. By using *o*-nitrobenzyl 2'-hydroxyl protection and phosphoramidite chem., a sufficient amt. of the oligoribonucleotides for NMR study were easily obtained in high yields. The structure of the duplex, which is formed by the oligomers and contains a G:U base pair, was examd. by NMR and CD spectroscopy.

110: 24234v **Use of trisdialkylaminophosphines for preparing deoxyribonucleoside 3'-phosphorbisamidites as effective reagents in a solid-phase synthesis of oligodeoxyribonucleotides.** Yamana, Kazushige; Nishijima, Yoshitaka; Nakano, Hidehiko; Sangen, Osamu (Dep. Appl. Chem., Himeji Inst. Technol., Himeji, Japan 671-22). *Nucleic Acids Symp. Ser.* 1988, 20, 81-2 (Eng). A report from the 15th symposium on nucleic acids chem. Use of tris(dialkylamino)phosphines for the in situ prepn. of deoxyribonucleoside phosphorbisamidites is described. The effectiveness of the bisamidites is demonstrated in the synthesis of oligodeoxyribonucleotides.

110: 24235w **Preparation of spin-labeled oligonucleotides and their spectroscopic behavior in solution.** Makino, Keisuke; Murakami, Akira; Nagahara, Shunji; Nakatsuji, Yuna; Takeuchi, Tamio (Fac. Text. Sci., Kyoto Inst. Technol., Kyoto, Japan 606). *Nucleic Acids Symp. Ser.* 1988, 20, 89-90 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. Di- and pentanucleotides spin-labeled with 4-amino-2,2,6,6-tetramethylpi=peridin-*N*-oxyl were prepd. by oxidn. of H-phosphonate intermediates in the presence of the spin-label. ESR spectra of the spin-labeled oligonucleotides were obtained. These indicated that the spin-labeled oligonucleotides could form duplex with other DNA.

110: 24236x **Phosphorothioate DNA: synthesis via improved hydrogen-phosphonate chemistry.** Andrus, Alex; Zon, Gerald (Appl. Biosyst., Foster City, CA 94404 USA). *Nucleic Acids Symp. Ser.* 1988, 20, 121-2 (Eng). A report from the 15th symposium on nucleic acids chem. held in 1988. An improved version of the hydrogen-phosphonate method of DNA synthesis utilizes an efficient capping agent, iso-Pr phosphite, and a stable activator, 1-adamanta=necarbonyl chloride. After synthesis, elemental sulfur converts the hydrogen-phosphonate linkages to phosphorothioates in one hour. Aq. iodine oxidn. generates the phosphodiester linkages. In either case, subsequent couplings are efficient, allowing the prodn. of oligonucleotides contg. both phosphorothioate and phsophodiester linkages, in defined sequences.